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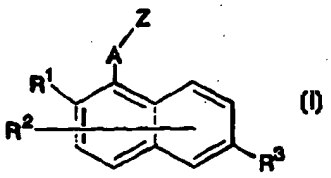
(54) Title: 5–AROYLNAPHTHALENE DERIVATIVES

(57) Abstract

The present invention relates to certain 5–aroylnaphthalene derivatives of formula (I), wherein A is a bond, $-CH_2-$, $-CH(OH)-$, $-C{=}NOR^4-$, $-C(O)-$, $-NR^5-$, $-O-$, or $-S(O)_n-$ where n is an integer from 0 to 2, R^4 is hydrogen or alkyl, and R^5 is hydrogen, alkyl, or acyl; Z is a group represented by formula (B), (C), (D), or (E), where n^1 is 0 to 3; X is O or S; R^6 and R^7 are independently selected from hydrogen, alkyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, acyl, alkylthio, cycloalkylthio, cycloalkylalkylthio, alkoxy, cycloalkyloxy, cycloalkylalkyloxy, halogenalkyloxy, alkenyl, halogen, cyano, nitro, hydroxy, or $-NR^9R^{10}$ where R^9 and R^{10} are independently hydrogen, alkyl, or acyl; or R^6 and R^7 when they are adjacent to each other form methylenedioxy or ethylenedioxy; R^8 is hydrogen, alkyl, halogenalkyl, alkoxy, cycloalkyloxy, halogenalkyloxy, alkylthio, cycloalkylthio, nitro, cyano, hydroxy, or halogen; R^1 is hydrogen, alkyl, alkenyl, alkynyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, halogenalkyloxy, hydroxyalkyloxy, alkoxyalkyloxy, alkylthio, cycloalkylthio, cycloalkylalkylthio, hydroxy, halogen, cyano, carboxy, alkoxycarbonyl, acyl, $-C{=}NOR^4$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-OCONR^9R^{10}$, or $-OSO_2R^{11}$ where R^4, R^9, and R^{10} are as previously defined and R^{11} is alkyl, cycloalkyl, or halogenalkyl; R^2 is hydrogen, alkyl, alkoxy, halogen, nitro, or $-NR^9R^{10}$; and R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ where R^{12} is alkyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, or alkoxycarbonylalkyl; R^{13} is hydrogen, alkyl, or acyl; and R^{14} is hydrogen, alkyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, amino, aminoalkyl, aryl, aralkyl, heteroaralkyl, heterocyclo, heterocycloalkyl, acyl, hydroxy, or alkoxy; or R^{13} and R^{14} together with the nitrogen atom to which they are attached optionally form a heterocycloamino group; that are inhibitors of prostaglandin G/H synthase, pharmaceutical compositions containing them, methods for their use, and methods for preparing these compounds.



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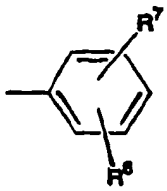

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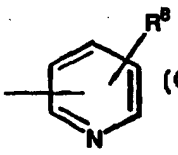

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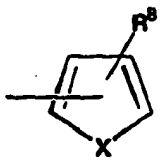

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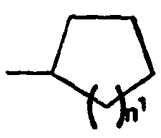

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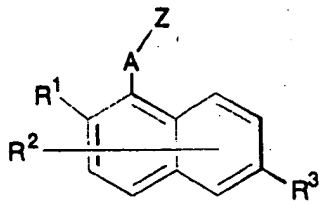
5-Aroylnaphthalene Derivatives

This invention relates to anti-inflammatory and analgesic compounds, especially to certain 5-aroylnaphthalene derivatives, pharmaceutical compositions containing them, methods for their use, and methods for preparing these compounds.

U.S. Patent No. 3,899,529 (Merck) discloses aroyl substituted naphthaleneacetic acids useful as anti-inflammatory agents, anti-pyretic, and analgesic agents.

U.S. Patent No. 3,755,455 (Sandoz) discloses (1-alkoxy-2-naphthyl)substituted or unsubstituted phenyketones useful as anti-inflammatory agents.

In a first aspect, this invention relates to compounds selected from the group of compounds represented by formula (I):



(I)

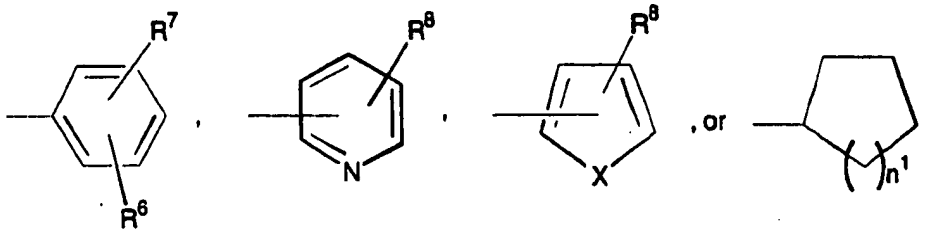
wherein:

A is a bond, $-CH_2-$, $-CH(OH)-$, $-C=NOR^4-$, $-C(O)-$, $-NR^5-$, $-O-$, or $-S(O)_n-$ where n

is an integer from 0 to 2, R^4 is hydrogen or alkyl, and R^5 is hydrogen,

alkyl, or acyl;

Z is a group represented by formula (B), (C), (D), or (E):



(B) (C) (D) (E)

where:

n^1 is 0 to 3;

X is O or S;

R^6 and R^7 are independently selected from hydrogen, alkyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, acyl, alkylthio, cycloalkylthio, cycloalkylalkylthio, alkoxy, cycloalkyloxy, cycloalkylalkyloxy, halogenalkyloxy, alkenyl, halogen, cyano, nitro, hydroxy, or $-NR^9R^{10}$ where R^9 and R^{10} are independently hydrogen, alkyl, or acyl; or

R^6 and R^7 when they are adjacent to each other form methylenedioxy or ethylenedioxy;

R^8 is hydrogen, alkyl, halogenalkyl, alkoxy, cycloalkyloxy, halogenalkyloxy, alkylthio, cycloalkylthio, nitro, cyano, hydroxy, or halogen;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, halogenalkyloxy, hydroxyalkyloxy, alkoxyalkyloxy, alkylthio, cycloalkylthio, cycloalkylalkylthio, hydroxy, halogen, cyano, carboxy, alkoxycarbonyl, acyl, $-C{=}NOR^4$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-OCONR^9R^{10}$, or $-OSO_2R^{11}$ where R^4, R^9, and R^{10} are as previously defined and R^{11} is alkyl, cycloalkyl, or halogenalkyl;

R^2 is hydrogen, alkyl, alkoxy, halogen, nitro, or $-NR^9R^{10}$; and

R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ where:

R^{12} is alkyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, or alkoxycarbonylalkyl;

R^{13} is hydrogen, alkyl, or acyl; and

R^{14} is hydrogen, alkyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, amino, aminoalkyl, aryl, aralkyl, heteroaralkyl, heterocyclo, heterocycloalkyl, acyl, hydroxy, or alkoxy; or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a heterocycloamino group; and

their pharmaceutically acceptable salts, prodrugs, individual isomers, and mixtures of isomers.

In a second aspect, this invention relates to pharmaceutical compositions comprising a pharmaceutically effective amount of a compound of formula (I) or its pharmaceutically acceptable salt and a pharmaceutically acceptable non-toxic excipient.

In a third aspect, this invention relates to the of treatment of a disease, in particular inflammatory and autoimmune diseases, in a mammal treatable by administration of a prostaglandin G/H synthase inhibitor, comprising administration of a therapeutically effective amount of a compound of formula (I) or its pharmaceutically acceptable salt.

In a fourth aspect, this invention relates to processes for preparing compounds of formula (I).

Definitions

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl, pentyl, and the like.

"Alkenyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing at least one double bond, e.g., ethenyl, 2-propenyl, and the like.

"Alkynyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing at least one triple bond, e.g., ethynyl, propynyl, butynyl, and the like.

"Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g., methylene, ethylene, propylene, 2-methylpropylene, pentylene, and the like.

"Cycloalkyl" means a cyclic saturated monovalent hydrocarbon radical of three to seven carbon atoms, e.g., cyclopropyl, cyclohexyl, and the like.

"Halogen" means fluoro, chloro, bromo, and iodo.

"Halogenalkyl" means alkyl substituted with one or more halogen atoms, preferably one to three halogen atoms, preferably fluorine or chlorine, including those substituted with different halogens, e.g., $-CH_2Cl$, $-CF_2$, $-CH_2CF_2$, $-CF_2CF_3$, $-CH_2CCl_3$, and the like.

"Alkoxy", "alkenyloxy", "cycloalkyloxy", or "halogenalkyloxy" means a radical -OR where R is alkyl, alkenyl, cycloalkyl, or halogenalkyl respectively as defined above, e.g., methoxy, ethoxy, propoxy, 2-propoxy, ethenyloxy, cyclopropyloxy, cyclobutyloxy, $-OCH_2Cl$, $-OCF_3$, and the like.

"Alkylthio" or "cycloalkylthio" means a radical -SR where R is alkyl or cycloalkyl respectively as defined above, e.g., methylthio, butylthio, cyclopropylthio, and the like.

"Acyl" means a radical -C(O)R where R is hydrogen, alkyl, or halogenalkyl as defined above, e.g., formyl, acetyl, trifluoroacetyl, butanoyl, and the like.

" Monosubstituted amino " means a radical -NHR where R is alkyl or acyl, e.g., methylamino, (1-methylethyl)amino, and the like.

"Disubstituted amino " means a radical -NRR' where R and R' are independently alkyl or acyl, e.g., dimethylamino, methylethylamino, di(1-methylethyl)amino, and the like.

"Hydroxyalkyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three or six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

"Alkoxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three or six carbons substituted with at least one alkoxy group as defined above, e.g., 2-methoxyethyl, 2-methoxypropyl, and the like.

"Hydroxyalkyloxy" or "alkoxyalkyloxy" means a radical -OR where R is hydroxyalkyl or alkoxyalkyl respectively as defined above, e.g., 2-hydroxyethyloxy, 2-methoxyethyloxy, and the like.

"Aminoalkyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three or six carbons substituted with at l ast one -NRR' where R and R' are independently selected from hydrogen, alkyl, or acyl, e.g., 2-aminoethyl, 2-N,N-diethylaminopropyl, 2-N-acetylamino-ethyl, and the like.

"Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 12 ring atoms and optionally substituted independently with one or more substituents, preferably one or two substituents, selected from alkyl, halogenalkyl, cycloalkyl, alkoxy, alkylthio, halogen, nitro, acyl, cyano, amino, monosubstituted amino, disubstituted amino, hydroxy, carboxy, or alkoxycarbonyl. More specifically the term aryl includes, but is not limited to, phenyl, biphenyl, 1-naphthyl and 2-naphthyl, and the derivatives thereof.

"Heteroaryl" means a monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms containing one or more, preferably one or two ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. The heteroaryl ring is optionally substituted independently with one or more substituents, preferably one or two substituents, selected from alkyl, halogenalkyl, cycloalkyl, alkoxy, alkylthio, halogen, nitro, acyl, cyano, amino, monosubstituted amino, disubstituted amino, hydroxy, carboxy, or alkoxycarbonyl. More specifically the term heteroaryl includes, but are not limited to, pyridyl, pyrrolyl, thienyl, furanyl, indolyl, quinolinyl and benzopyranyl, and the derivatives thereof.

"Heterocycloamino" means a saturated monovalent cyclic group of 5 to 8 ring atoms, wherein at least one ring atom is N and optionally contains a second ring heteroatom selected from the group consisting of N, O, or $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C (e.g., morpholino, thiomorpholino, piperidino, piperazino, pyrrolidino, and the like). The heterocycloamino ring may be optionally fused to a benzene ring or it may be optionally substituted

independently with one or more substituents, preferably one or two substituents, selected from alkyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, halogen, cyano, acyl, amino, monosubstituted amino, disubstituted amino, carboxy, or alkoxycarbonyl. More specifically the term heterocycloamino includes, but is not limited to, pyrrolidino, piperidino, morpholino, piperazino and thiomorpholino and the derivatives thereof.

"Heterocyclo" means a saturated monovalent cyclic group of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or $S(O)_n$, where n is an integer from 0 to 2, the remaining ring atoms being C. The heterocyclo ring may be optionally fused to a benzene ring or it may be optionally substituted independently with one or more substituents, preferably one or two substituents, selected from alkyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, halogen, cyano, acyl, monosubstituted amino, disubstituted amino, carboxy, or alkoxycarbonyl. More specifically the term heterocyclo includes, but is not limited to, piperidino, piperazino, pyrrolidino, morpholino, tetrahydropyranyl and thiomorpholino, and the derivatives thereof.

"Cycloalkylalkyl" means a radical $-R^aR^b$ where R^a is an alkylene group and R^b is a cycloalkyl group as defined above e.g., cyclopropylmethyl, cyclohexylpropyl, 3-cyclohexyl-2-methylpropyl, and the like.

"Cycloalkylalkyloxy" means a radical -OR where R is a cycloalkylalkyl group as defined above e.g., cyclopropylmethyloxy, 3-cyclohexylpropyloxy, and the like.

"Aralkyl" means a radical $-R^aR^b$ where R^a is an alkylene group and R^b is an aryl group as defined above e.g., benzyl, phenylethyl, 3-(3-chlorophenyl)-2-methylpentyl, and the like.

"Heteroaralkyl" means a radical -R^aR^b wher R^a is an alkylene group and R^b is a heteroaryl group as defined above e.g., 2-,3-, or 4-pyridylmethyl, furan-2-ylmethyl and the like.

"Heterocycloalkyl" means a radical -R^aR^b where R^a is an alkylene group and R^b is a heterocyclo group as defined above e.g., morpholin-4-ylethyl, tetrahydrofuran-2-ylmethyl and the like.

"Pro-drugs" means any compound which releases an active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound of formula (I) in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group in compound (I) is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of formula (I), and the like.

Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed „isomers". Isomers that differ in the arrangement of their atoms in space are termed „stereoisomers".

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (*R*)- or (S)- stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the

separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of „Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:
(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzene-sulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis- (3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or
(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an

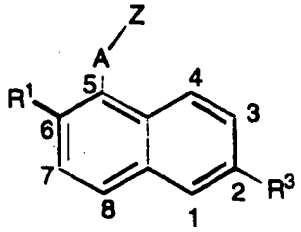
organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine, and the like.

A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

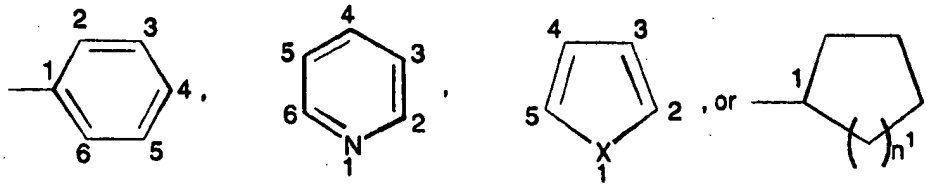
"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry i.e., an atom or group capable of being displaced by a nucleophile and includes halogen, alkanesulfonyl-oxy, arenesulfonyloxy, ester, or amino such as chloro, bromo, iodo, mesyloxy, tosyloxy, trifluorosulfonyloxy, methoxy, N,O-dimethyl-hydroxylamino, and the like.

Nomenclature

The naming and numbering of the compounds of this invention is illustrated below. The naphthalene nucleus of the compounds of formula (I) are numbered as follows:



Side chains of the Z substituent are numbered as shown below:



(B) (C) (D) (E)

The pyridine, thiophene, and furan rings can be linked to A at any position on the ring other than 1-position. Accordingly, the pyridine ring can be 2-, 3-, or 4-pyridyl, the thiophene ring can be 2- or 3-thienyl, and the furan ring can be 2- or 3-furyl.

The nomenclature used in this application is generally based on the IUPAC recommendations.

Preferred embodiments of compounds of formula (I) as defined in the first aspect of the invention are as follows:

(i) One preferred group of compounds is that wherein:
A is -C(O)-.

(ii) A second preferred group of compounds is that wherein:
A is -C=NOR^4- where R^4 is hydrogen or alkyl.

(iii) A third preferred group of compounds is that wherein:
A is -O-, -S-, or -NR^5- where R^5 is hydrogen, alkyl, or acyl.

Preferably, any of these groups may be combined with a group Z being (B) or (D), most preferred A is -C(O)-.

In a preferred embodiment R^3 is -SO_2R^{12} where preferably R^{12} is alkyl, more preferably methyl, or R^3 is -SO_2NR^{13}R^{14} where preferably R^{13} is hydrogen and R^{14} is hydrogen, methyl, 2-hydroxyethyl, or hydroxy, more preferably R^{14} is hydrogen.

Within these preferred groups a more preferred group of compounds is that wherein:

Z is represented by formula (B) where R^6 and R^7 are independently selected from hydrogen, alkyl, cycloalkyl, alkoxy, ethenyl, halogen, or -NR^{9}R^{10} where R^9 and R^{10} are alkyl, preferably methyl, more preferably R^6 and R^7 are hydrogen, alkyl, alkoxy, or halogen, most preferably hydrogen, methyl, methoxy, fluoro, or chloro; and R^2 is hydrogen. Preferably, R^6 is at the 2- or 3-position and R^7 is at the 4-position.

Another more preferred group of compounds is that wherein Z is represented by formula (D) where X is S and R^8 and R^2 are hydrogen. Preferably S is linked to A at the 2-position of (D).

Within these preferred and more preferred groups a particularly preferred group of compounds is that wherein:

R^1 is preferably hydrogen, alkyl, alkoxy, cycloalkyloxy, hydroxyalkyloxy, hydroxy, halogen or cyano, more preferably hydrogen, methyl, methoxy, cyclopropyloxy, 2-hydroxyethyloxy, hydroxy, chloro, or cyano, most preferably hydrogen, methyl, methoxy, hydroxy, chloro, or cyano.

A particularly preferred group of compounds is that wherein:

R^1 is hydrogen, alkyl, alkoxy, cycloalkyloxy, hydroxyalkyloxy (preferably 2-hydroxyethyloxy), hydroxy, halogen or cyano, more preferably hydrogen, methyl, methoxy, cyclopropyloxy, 2-hydroxyethyloxy, hydroxy, chloro, or cyano, most preferably hydrogen, methyl, methoxy, hydroxy, chloro, or cyano; and R^3 is $-SO_2R^{12}$ where R^{12} is alkyl, preferably methyl, or R^3 is $-SO_2NR^{13}R^{14}$ where R^{13} is hydrogen and R^{14} is hydrogen, methyl, 2-hydroxyethyl, or hydroxy, more preferably R^{14} is hydrogen. Most preferred R^1 is hydrogen, methyl, methoxy, hydroxy, chloro or cyano and R^3 is $-SO_2Me$ or $-SO_2NH_2$.

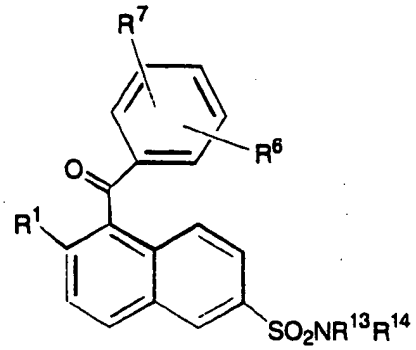
Particularly preferred compounds of the present invention are:

5-(4-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide.
5-(4-methylbenzoyl)-6-methoxy-2-naphthalenesulfonamide.
5-(2-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide.
5-(3-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide.
5-(4-fluorobenzoyl)-6-methoxy-2-methylsulfonylnaphthalene.
5-(4-fluorobenzoyl)-6-hydroxy-2-methylsulfonylnaphthalene.
5-benzoyl-6-hydroxy-2-methylsulfonylnaphthalene.
5-benzoyl-6-methoxy-2-methylsulfonylnaphthalene.
5-benzoyl-6-cyano-2-napthalenesulfonamide.
5-(4-fluorobenzoyl)-6-cyano-2-naphthalenesulfonamide.
5-(4-fluorobenzoyl)-6-methyl-2-naphthalenesulfonamide.

5-(4-fluorobenzoyl)-6-chloro-2-naphthalenesulfonamide.
5-(2-fluorobenzoyl)-6-cyano-2-naphthalenesulfonamide.
5-(2-fluorobenzoyl)-6-hydroxy-2-naphthalenesulfonamide.
5-(2-fluorobenzoyl)-6-chloro-2-naphthalenesulfonamide.
5-(2-fluorobenzoyl)-6-methyl-2-naphthalenesulfonamide.
5-(4-methylbenzoyl)-6-cyano-2-naphthalenesulfonamide.
5-(4-fluorobenzoyl)-6-cyano-2-methylsulfonylnaphthalene.
5-benzoyl-6-cyano-2-methylsulfonylnaphthalene.
5-(4-chlorobenzoyl)-6-cyano-2-methylsulfonylnaphthalene.
5-(2-fluorobenzoyl)-6-cyano-2-methylsulfonylnaphthalene.

Representative compounds of this invention are as follows:

I. Compounds of formula (I) where A is -C(O)-, Z= group represented by formula (B), R^2 = hydrogen, and R^3 is at the 2-position wherein $R^3 = -SO_2NR^{13}R^{14}$ and the other groups are as defined below are:



CPD #	R^1	R^6	R^7	R^{13}	R^{14}	M. Pt. °C	Mass. Spec. m/e
1	OMe	H	4-F	H	H	172.2-172.8	
2	OH	H	4-F	H	H	166.5-166.9	
3	OMe	H	4-F	H	acetyl	foam	401

4	OMe	H	4-Me	H	H	203-203.5	
5	OC_2H_5	H	4-F	H	H	138.8-139.7	
6	OMe	H	4-Cl	H	H	188.1-188.7	
7	OMe	H	4-F	H	*n*-C_4H_9		415
8	OMe	H	4-F	H	2-methoxyethyl		417
9	OMe	H	4-F	H	2-propyl		401
10	OMe	H	4-F	H	2-hydroxyethyl		403
11	OMe	H	4-F	H	*t*-butyl		415
12	OMe	H	4-F	Me	Me		387
13	OMe	H	3-Cl	H	H		375
14	OMe	H	2-F	H	H		359
15	OMe	H	3-F	H	H		359
16	OMe	H	2-Me	H	H		355
17	OMe	H	2-Br	H	H		419
18	OMe	H	3-Br	H	H		419
19	OMe	2-Cl	4-Cl	H	H		409
20	OMe	2-F	4-F	H	H		377
21	OMe	2-Cl	4-F	H	H		393
22	OMe	H	4-F	H	Me		373
23	OMe	H	H	H	H	151.5-151.9	
24	OMe	H	4-F	H	benzyl		449
25	OMe	H	4-F	H	ethyl		387
26	OMe	H	4-F	H	2-phenylethyl		463
27	OMe	H	4-F	*n*-pentyl	*n*-pentyl		499
28	OMe	H	4-F	H	*n*-propyl		401
29	OMe	H	4-F	H	3-hydroxypropyl		417
30	OMe	H	4-F	H	2-(morpholin-4-yl)ethyl		472

31	OMe	H	4-F	H	3-(morpholin-4-yl)propyl		486
32	OMe	H	4-F	H	pyridin-2-ylmethyl		450
33	OMe	H	4-F	H	pyridin-4-ylmethyl		450
34	OMe	H	4-F	H	2-(pyridin-4-yl)ethyl		464
35	OMe	H	4-F	H	1-(*RS*)-(hydroxy-methyl)ethyl		417
36	OMe	H	4-F	ethyl	ethyl		415
37	OMe	H	4-F	H	furan-2-ylmethyl		439
38	OMe	H	4-F	H	cyclopropyl		399
39	OMe	H	4-F	H	cyclohexyl		441
40	OMe	H	2-Cl	H	H		375
41	OMe	2-F	4-CF_3	H	H		427
42	OMe	2-CF_3	4-F	H	H		427
43	OMe	2-Cl	6-Cl	H	H		409
44	OMe	H	4-CF_3	H	H		409
45	OMe	H	3-Me	H	H		355
46	OMe	H	4-*t*-butyl	H	H		397
47	OMe	2-F	4-Cl	H	H		393
48	OMe	2-Cl	4-Br	H	H		453
49	OMe	3-Cl	4-Cl	H	H		409
50	OMe	H	4-Br	H	H		419
51	OMe	H	4-MeS	H	H		387
52	OMe	2-F	6-F	H	H		377
53	OMe	H	4-F	H	4-(N,N-diethyl-amino)-1-(*RS*)-methylbutyl		500
54	OMe	H	4-F	H	1-(*RS*)-(hydroxy-methyl)-2-methyl-propyl		445
55	OMe	H	4-F	H	1-(*S*)-phenylethyl		513
56	OMe	H	4-F	H	1-(*R*)-phenylethyl		463

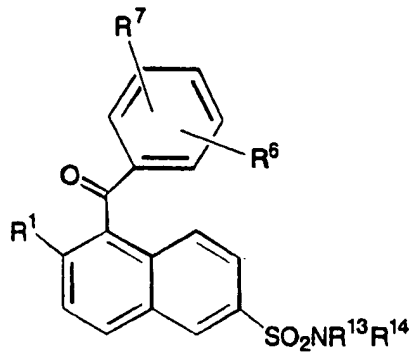
57	OMe	H	4-F	H	methoxycarbonyl-methyl		431
58	OMe	H	4-F	H	2-methyl-2-propenyl		413
59	OMe	H	4-F	H	1-benzylpiperidin-4-yl		532
60	OMe	H	4-F	Me	1-(1,4-benzodioxan-2-yl-methyl)piperidin-4-yl		604
61	OMe	3-Cl	5-Cl	H	H		409
62	OMe	H	4-OH	H	H	225-225.6	
63	H	H	4-F	H	H	189.9-190.5	
64	CN	H	4-F	H	H	192.1-192.9	
65	Me	H	4-F	H	H	175.5-177	
66	Cl	H	4-F	H	H	229.6-229.8	
67	CN	H	2-F	H	H		354
68	OSO_2CF_3	H	4-F	H	H		478
69	$C(O)NH_2$	H	4-F	H	H		372
70	OSO_2Me	H	4-F	H	H		423
71	OH	H	2-F	H	H	194.4-195.7	
72	OMe	H	3-NO_2	H	H	213.5-214	
73	CN	2-F	4-F	H	H		
74	$OCONMe_2$	H	4-F	H	H	202.6-203.1	
75	OMe	H	3-NH_2	H	H .HCl	238.9-240.3	

76	OMe	H	4-MeO	H	H	173.7-174.1	
77	OMe	H	4-NO_2	H	H	225.2-225.9	
78	2-hydroxy-ethoxy	H	4-F	H	H	Foam	
79	COOH	H	4-MeO	H	H		385
80	OH	2-F	6-F	H	H		363
81	COOH	H	4-OH	H	H		371
82	OMe	H	4-NH_2	H	H	277.3-277.7	
83	OMe	H	4-F	H	3-(pyrrolidin-2-one)propyl		484

and are named as:

1. 5-(4-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide.
4. 5-(4-methylbenzoyl)-6-methoxy-2-naphthalenesulfonamide.
10. N-(2-hydroxyethyl)-5-(4-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide.
14. 5-(2-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide.
15. 5-(3-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide.
30. N-[2-(morpholin-4-yl)ethyl]-5-(4-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide.
41. 5-(2-fluoro-4-trifluoromethylbenzoyl)-6-methoxy-2-naphthalenesulfonamide.
51. 5-(4-methylthiobenzoyl)-6-methoxy-2-naphthalenesulfonamide.
64. 5-(4-fluorobenzoyl)-6-cyano-2-naphthalenesulfonamide.
79. 5-(4-methoxybenzoyl)-6-carboxy-2-naphthalenesulfonamide.

II. Compounds of formula I where A is -C(O)-, Z= group represented by formula (B), R^2 = hydrogen, and R^3 is at the 2-position wherein R^3 = $-SO_2NR^{13}R^{14}$ and the other groups are as defined below are:



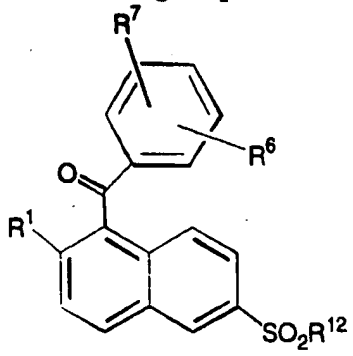
CPD #	R^1	R^6	R^7	$NR^{13}R^{14}$	Mass. Spec. m/e
84	OMe	H	4-F	4-methylpiperazino	442
85	OMe	H	4-F	4-phenylpiperazino	504
86	OMe	H	4-F	pyrrolidino	413
87	OMe	H	4-F	morpholino	429
88	OMe	H	4-F	piperidino	427
89	OMe	H	4-F	4-(4-fluorophenyl)-piperazino	522
90	OMe	H	4-F	2(*R*),6(S)-dimethyl-morpholino	457

and are named as:

84. 5-(4-fluorobenzoyl)-6-methoxy-2-(4-methylpiperazin-1-ylsulfonyl)-naphthalene.

88. 5-(4-fluorobenzoyl)-6-methoxy-2-(piperidin-1-ylsulfonyl)-naphthalene.

III. Compounds of formula I where A is -C(O)-, Z= group represented by formula (B), R^2 = hydrogen, and R^3 = $-SO_2R^{12}$ is at the 2-position and the other groups are as defined below are:

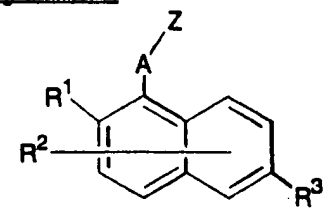


CPD #	R^1	R^6	R^7	R^{12}	M.Pt. °C	Mass. Spec. m/e
91	OMe	H	4-F	Me	foam	358
92	OH	H	4-F	Me	174.9-176	
93	OH	H	H	Me	oil	326
94	OMe	H	H	Me	oil	340
95	H	H	4-F	Me	162-163	
96	CN	H	4-F	Me	173.5-174.1	
97	CN	H	H	Me	181.5-182	
98	Cl	H	H	Me	133.1-133.4	
99	CN	H	2-F	Me	159.7-160.2	
100	Cl	H	4-Cl	Me	168.8-169.8	
101	Me	H	2-F	Me	131.5-131.8	
102	H	H	H	Me	82-86.5	
103	OMe	H	4-Me	Me	88.4-123.4	
104	CN	H	4-Cl	Me	183.5-184.4	
105	CN	H	4-Me	Me	183.7-184.1	
106	OCH_2CONMe_2	H	4-F	Me		429
107	$O(CH_2)_2OH$	H	4-F	Me		381
108	$CONH_2$	H	H	Me	223.4-224.3	
109	$CONH_2$	H	4-F	Me	223.4-224.3	

and are named as:

91. 5-(4-fluorobenzoyl)-6-methoxy-2-methylsulfonylnaphthalene.
92. 5-(4-fluorobenzoyl)-6-hydroxy-2-methylsulfonylnaphthalene.
93. 5-benzoyl-6-methoxy-2-methylsulfonylnaphthalene.
94. 5-benzoyl-6-methoxy-2-methylsulfonylnaphthalene.
96. 5-(4-fluorobenzoyl)-6-cyano-2-methylsulfonylnaphthalene.
97. 5-benzoyl-6-cyano-2-methylsulfonylnaphthalene.
99. 5-(2-fluorobenzoyl)-6-cyano-2-methylsulfonylnaphthalene.
104. 5-(4-chlorobenzoyl)-6-cyano-2-methylsulfonylnaphthalene.
107. 5-(4-fluorobenzoyl)-6-hydroxyethyloxy-2-methylsulfonyl-naphthalene.

IV. Miscellaneous compounds:



CPD #	A	Z	R^1	R^2	R^3	M.Pt. °C	Mass. Spec. m/e
110	$-CH_2-$	4-fluorophenyl	OMe	H	$-SO_2NH_2$	165.1-167	
111	-C(O)-	thiophen-2-yl	OMe	H	$-SO_2NH_2$		347
112	-C(O)-	furan-3-yl	OMe	H	$-SO_2NH_2$		331
113	$-SO_2-$	4-fluorophenyl	OMe	H	$-SO_2Me$	205.9-206.2	

and are named as:

110. 5-(4-fluorobenzyl)-6-methoxy-2-naphthalenesulfonamide.
113. 5-(4-fluorophenylsulfonyl)-6-methoxy-2-methylsulfonyl-naphthalene.

GENERAL SYNTHETIC SCHEME

Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, WI), Bachem (Torrance, CA), or Sigma (St. Louis, MO) or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis*, Volumes 1-17 (John Wiley and Sons, 1991); *Rodd's Chemistry of Carbon Compounds*, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); *Organic Reactions*, Volumes 1-40 (John Wiley and Sons, 1991), *March's* Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and *Larock's* Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

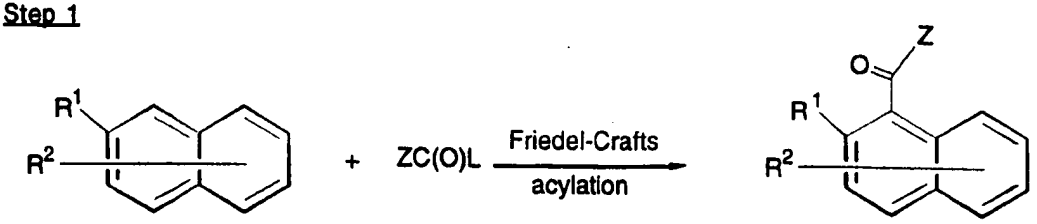
Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78 °C to about 150 °C, more preferably from about 0 °C to about 125 ° C and most preferably at about room (or ambient) temperature, e.g., about 20 °C.

Preparation of Compounds of Formula I

Scheme A describes the synthesis of a compound of formula (I) where A is -C(O)- and R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ from a naphthalene of formula 1 where R^1 is an ortho-para directing group.

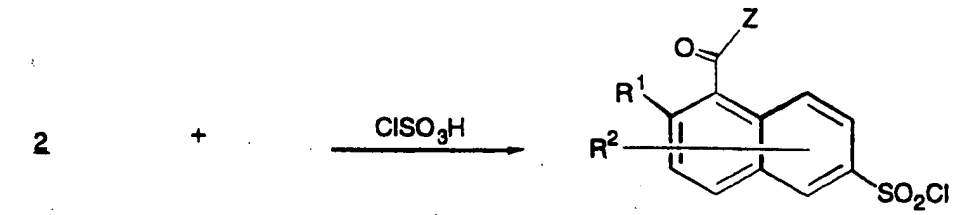
Scheme A

Step 1



1 2

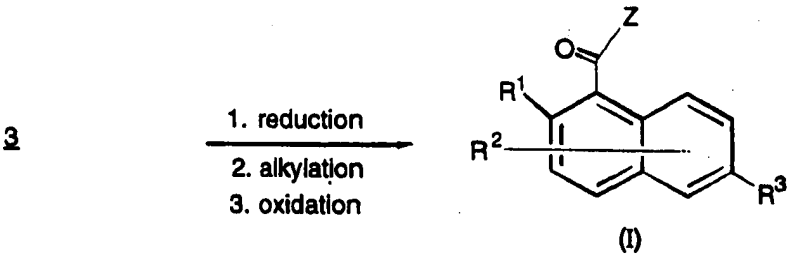
Step 2



3

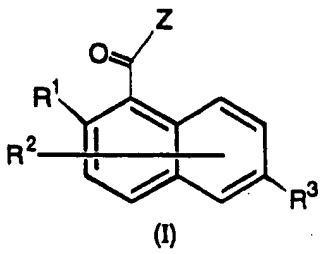
Step 3

Method A: Synthesis of compound (I) where R^3 is $-SO_2R^{12}$



(I)

Method B: Synthesis of compound (I) where R^3 is $-SO_2NR^{13}R^{14}$



(I)

In step 1, a 5-aroylnaphthalene of formula 2 is prepared by acylating a naphthalene of formula 1, with an acylating agent ZC(O)L, where Z is as defined in the Summary of the Invention and L is a leaving group under Friedel-Crafts acylating conditions (e.g., halogen, preferably chloro). The reaction is carried out in the presence of a Lewis acid such as aluminum chloride, tin chloride, and the like. Suitable solvents for the reaction are halogenated hydrocarbons such as dichloromethane, dichloroethane, and the like. In general, the compounds of formula 1 and the acid halides are commercially available or can readily be synthesized by those of ordinary skill in the art.

In step 2, a 5-aroylnaphthalene-2-sulfonyl chloride of formula 3 is prepared by reacting the compound of formula 2 with chlorosulfonic acid. The sulfonylation reaction can be carried out either in neat chlorosulfonic acid or in halogenated hydrocarbons such as dichloromethane and the like.

In step 3, a compound of formula (I) where R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ is prepared from the 5-aroylnaphthalene-2-sulfonyl chloride 3 by following method A or method B respectively, as described below.

In method A, compound (I) where R^3 is $-SO_2R^{12}$ is prepared by carrying out reduction, alkylation, and oxidation steps on compound 3. The reduction of the sulfonyl chloride group to the thiol is carried out

in the presence of triphenylphosphine by following the procedure described in Oae, S. and Togo, H., *Bull. Chem. Soc. Jpn.*, **56**, 3802, (1983). The thiol is alkylated to give the thioether by reacting it with an alkylating agent $R^{12}L$ where R^{12} is as defined in the Summary of the Invention and L is a leaving group under alkylating conditions, (e.g.; halogen, methanesulfonate, p-toluenesulfonate, and the like). The alkylation reaction is carried out in the presence of a non-nucleophilic base (e.g., cesium carbonate, sodium hydride, or potassium carbonate) and in a suitable polar aprotic organic solvent (e.g., ether, tetrahydrofuran, dioxane, dimethylformamide, and the like). The thioether is then oxidized to the sulfone with a suitable oxidizing agent such as m-chloroperoxybenzoic acid, sodium periodate, potassium hydrogen persulfate, sodium hypochlorite, and the like.

In method B, compound (I) where R^3 is $-SO_2NR^{13}R^{14}$ is prepared by reacting the 2-naphthalenesulfonyl chloride 3 with an excess amount of an amine of formula $NHR^{13}R^{14}$ in a suitable organic solvents (e.g., dioxane, tetrahydrofuran, and the like). Also, compound (I) where R^{13} and/or R^{14} are hydrogen can be alkylated/acylated to a corresponding compound of formula (I) where R^{13} and/or R^{14} are not hydrogen, if desired, by reacting it with a suitable alkylating or acylating agent, in the presence of a base (e.g., sodium carbonate, sodium hydride, triethylamine, and the like) and in a polar aprotic solvent such as methylene chloride, dioxane, and the like.

The preparation of a compound of formula (I) where A is -C(O)-, Z is 4-fluorophenyl, R^1 is -OMe, and R^3 is $-SO_2NH_2$ by this method is described in Example 1.

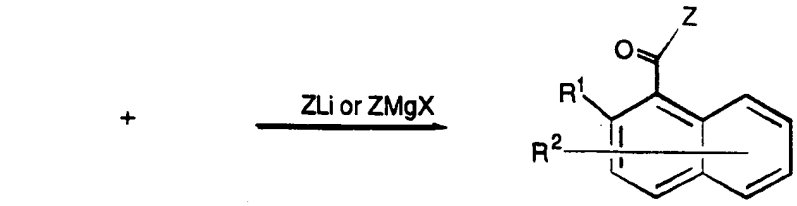
Scheme B describes the synthesis of a compound of formula (I) where A is -C(O)- and R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ from a 1-naphthoic acid 4 where R^1 is an ortho-para directing group.

Scheme B

Step 1

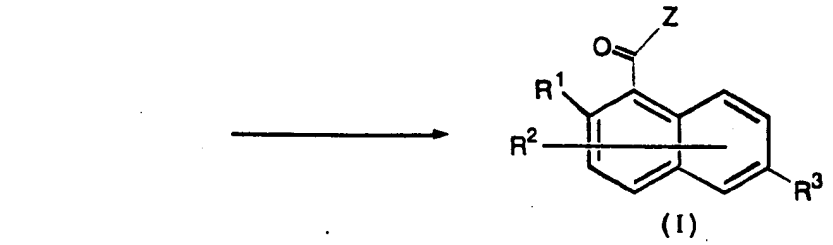
4 5

Step 2



2

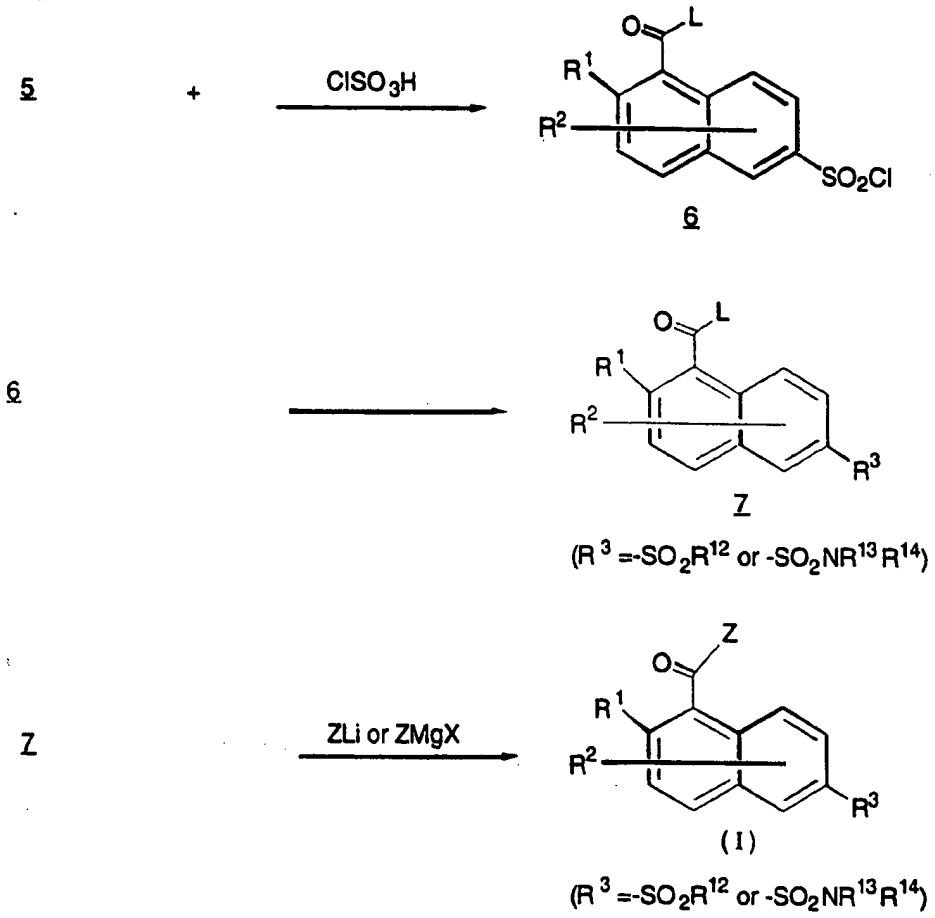
Step 3



(I)

(R^3 =-SO_2R^{12} or -$SO_2NR^{13}R^{14}$)

Step 2 (Alternative)



In Step 1, an acid derivative of formula 5 where L is a leaving group under organometallic displacement reaction conditions [e.g., alkoxy (preferably methoxy or ethoxy), dialkylamino, or preferably N,O-dimethylhydroxylamino] is prepared from a 1-naphthoic acid of formula 4 by methods well known in the field of organic chemistry. For example, compound 5 where L is a N,O-dimethylhydroxylamino group can be prepared by first forming the acid chloride derivative of 4 with a suitable chlorinating agent such as oxalyl chloride, followed by treatment with N,O-dimethyl-hydroxylamine hydrochloride in the presence of an organic base such as triethylamine. Generally, the 1-naphthoic acids 4 are commercially available.

In Step 2, a 1-aroylnaphthalene of formula 2 is prepared by reacting 5 with an organometallic reagent such as a Grignard reagent or an organolithium reagent (ZMgX or ZLi) under the reaction conditions such as those described in Takei, M., *Chem. Lett.*, 687 (1974) and Nahm, S., Weinreb, A. M., *Tet. Lett.*, **22**, 3815, (1981).

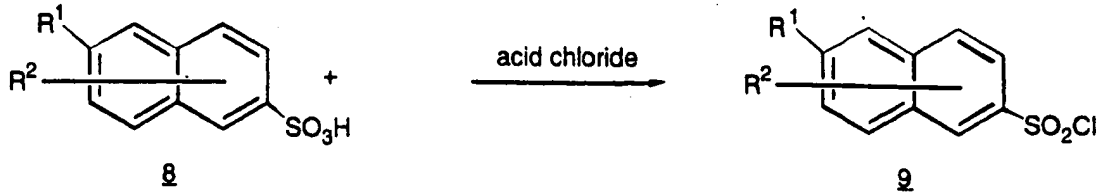
In Step 3, compound 2 is converted to a compound of formula (I) where R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ by proceeding as described in Scheme A, Steps 2 and 3.

Alternatively, compound (I) where R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ is prepared as shown in Step 2 (alternative), by first preparing a 2-naphthalenesulfone or a 2-naphthalene-sulfonamide of formula 7 from the acid derivative 5, utilizing the reaction conditions described in Scheme A, Steps 2 and 3. Compound 7 is then converted to a corresponding compound of formula (I), by proceeding as described in Scheme B, Step 2 above.

Scheme C describes the synthesis of a compound of formula (I) where A is -C(O)- and R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ from a naphthalenesulfonic acid 8 where R^1 is an ortho-para directing group.

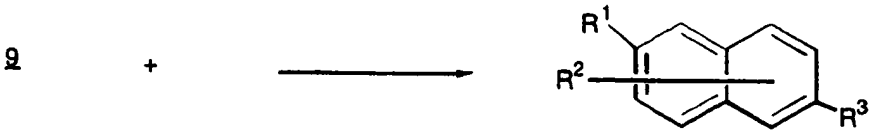
Scheme C

Step 1



8 9

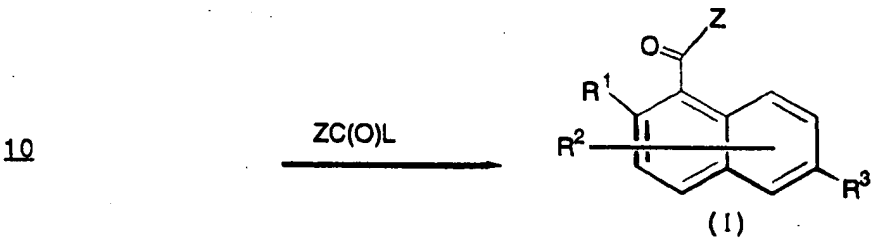
Step 2



10

(R^3 =-SO_2R^{12} or -$SO_2NR^{13}R^{14}$)

Step 3



(I)

(R^3 =-SO_2R^{12} or -$SO_2NR^{13}R^{14}$)

In Step 1, a 2-naphthalenesulfonyl chloride of formula 9 is prepared by reacting the 2-naphthalenesulfonic acid with an acid chloride such as thionyl chloride or oxalyl chloride.

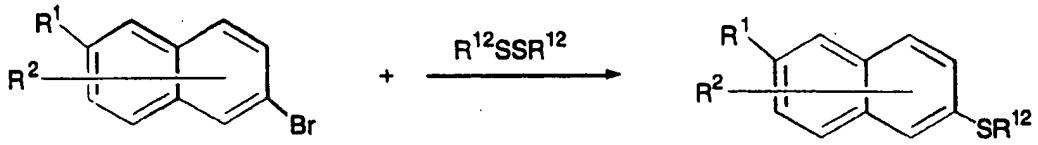
In Step 2, a 2-naphthalenesulfone or a 2-naphthalenesulfonamide of formula 10 is prepared from compound 9 by proceeding as described in Scheme A, Step 3.

In Step 3, compound 10 is acylated at the 5-position to give a compound of formula (I) where R^3 $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ by proceeding as described in Scheme A, Step 1.

Scheme D describes the synthesis of compounds of formula (I) where A is -C(O)- and R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ from bromonaphthalenes 11 where R^1 is an ortho-para directing group.

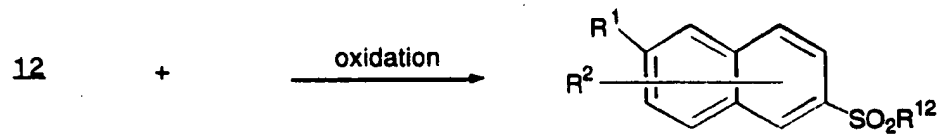
Scheme D

Step 1



11 12

Step 2

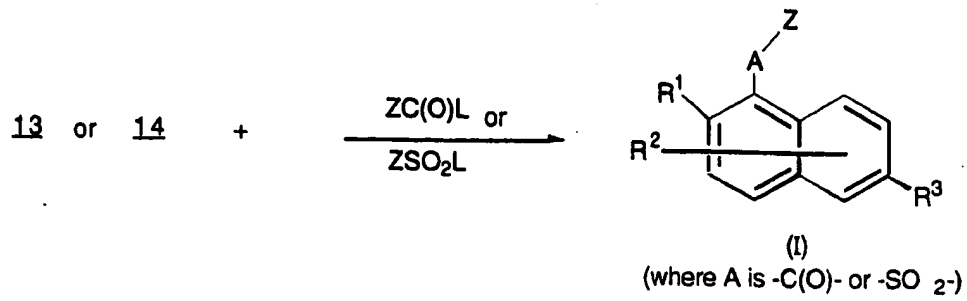


13

Step 3

14

Step 4



(I)
(where A is -C(O)- or -SO 2-)

In Step 1, a naphthalene thioether of formula 12 is prepared by reacting a bromonaphthalene of formula 11 with a disulfide $R^{12}SSR^{12}$ or $R^{12}SO_2SR^{12}$ (where R^{12} is as defined in the Summary of the invention) under an inert atmosphere. The nucleophilic substitution reaction can be carried out either stepwise by first conversion of the bromonaphthalene to an organometallic reagent, followed by treatment with a strong base such as *n*-butyllithium or directly in the presence of a copper catalyst such as copper powder, copper iodide, and the like. Suitable solvents for the reaction are polar aprotic solvents such as tetrahydrofuran, dimethylformamide, hexamethylphosphoramide, and the like.

In Step 2, the thioether 12 is oxidized to the naphthalenesulfone 13 by proceeding as described in Scheme A, Step 3, method A.

In Step 3, compound 13 (where R^{12} is methyl) can optionally be converted to a corresponding sulfonamide where R^{13} and R^{14} are hydrogen by following the literature procedure described in Huang, H., *et al*, *Tet. Lett.*, 7201, (1995). This sulfonamide can be alkylated to give the corresponding mono- or di- N-alkylated derivatives by utilizing the reaction conditions described in Scheme A, Step 3, method B.

In Step 4, the naphthalenesulfone 13 or the sulfonamide 14 is acylated or sulfonylated at the 5-position (when R^1 is an ortho-para directing group) to give a compound of Formula (I) where A is -C(O)-

or $-SO_2-$ and R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ by proceeding as described in Scheme A, Step 1.

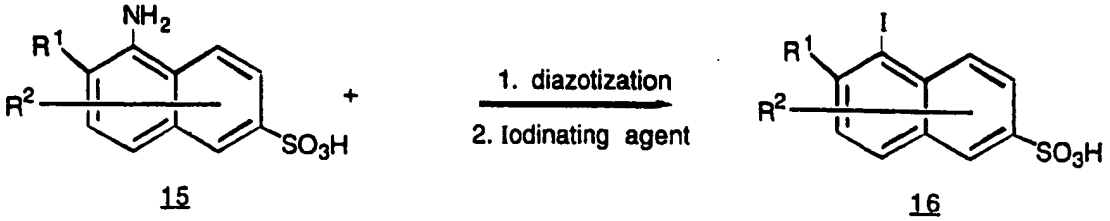
The preparation of compounds of formula (I) where A is -C(O)- or $-SO_2-$, Z is 4-fluorophenyl, R^1 is OMe, and R^3 is $-SO_2Me$ by this method are described in Example 2 and 3.

The preparation of compounds of formula (I) where A is -C(O)- , Z is 4-fluorophenyl, R^1 is -CN, and R^3 is $-SO_2Me$ by this method are described in Example 6.

Scheme E describes the synthesis of compounds of formula (I) where A is a bond, -O-, $-NR^5-$, or $-S(O)_n-$ where n is an integer from 0 to 2, R^5 is hydrogen or alkyl, and R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ from 5-amino-2-naphthalenesulfonic acids 15.

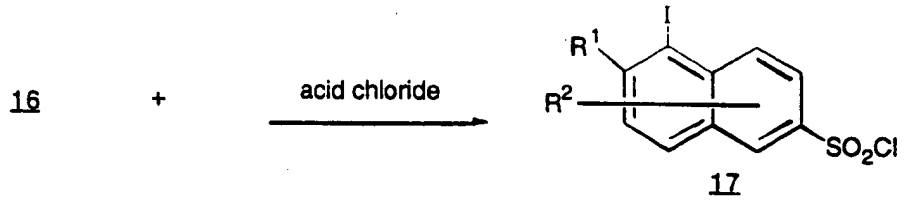
Scheme E

Step 1



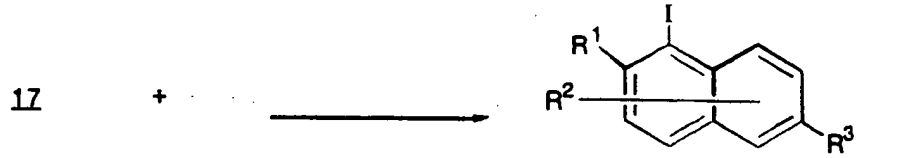
15 16

Step 2



17

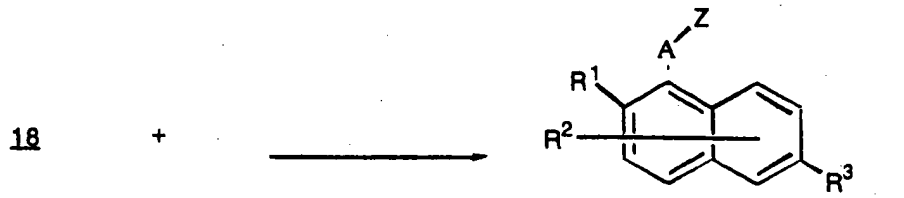
Step 3



18

(R^3 =-SO_2R^{12} or -$SO_2NR^{13}R^{14}$)

Step 4



(I)

(A = bond, -NR^5-, -O-, or -$S(O)_n$-)
(R^3 =-SO_2R^{12} or -$SO_2NR^{13}R^{14}$)

In Step 1, a 5-iodo-2-naphthalenesulfonic acid of formula 16 is prepared by converting a 5-amino-2-naphthalenesulfonic of formula 15 to a diazonium salt, which upon treatment with an iodinating reagent (e.g., I_2 or KI) gives the 5-iodo compound. This conversion can be carried out by utilizing the reaction conditions described in Heaney, H.

and Millar. I. T., *Org. Synth.*, **40**, 105, (1960). 5-Amino-2-naphthalenesulfonic acid is commercially available or can be prepared by nitration of the corresponding naphthalenesulfonic acid followed by reduction of the nitro group to an amine.

In Step 2, a 5-iodo-2-naphthalenesulfonyl chloride of formula 17 is prepared from the 5-iodo-2-naphthalenesulfonic acid 16 by utilizing the reaction conditions described in Scheme C, Step 1.

In Step 3, a 5-iodo-2-naphthalene of formula 18 where R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ are prepared from compound 17 by utilizing the reaction conditions described in Scheme A, Step 3, methods A or B respectively.

In Step 4, compounds of formula 18 are converted to compounds of formula (I) where A is a bond, $-NR^5-$ (where R^5 is hydrogen or alkyl), -O-, or -S- by following published literature procedures. Where A is a bond , *see*, Stille, J. K., *Agnew. Chem. Intl. Ed.*, **25**, 508, (1980), McKean, D. R., Parrinello, G., Renaldo, A. F., and Stille, S. K., *J. Org. Chem.*, **52**, 422, (1987) and Suzuki, *Syn. Commun.*, **11**, 513, (1981). Where A is a $-NR^5-$ (where R^5 is hydrogen or alkyl), -O- or -S- , *see*, Yamamoto, T., *Can. J. Chem.*, **61**, 86, (1983); Burnell, J. F., *Chem. Rev.*, **49**, 392, (1951); and Campbell, J. R., *J. Org. Chem.*, **29**, 1830, (1964) and Tesafaferri, L., Tiecco, M., Tingol, M., Chianelli, D., and Menfanucci, M., *Synthesis.*, 751, (1983) respectively.

Additional Processes

Compounds of formula (I) can also be prepared by modification of a group present on a corresponding compound of formula (I). For example, a compound of formula (I) where R^1 is hydroxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, halogenalkyloxy, $-OCONR^9R^{10}$ or $-OSO_2R^{11}$ may be prepared by de-alkylation of an alkoxy substituent on the corresponding compound of formula (I) followed by treatment with an appropriate alkylating, acylating or sulfonylating agents. The transformation can be carried out by methods well known in the field

of organic chemistry. Compounds of formula (I) where R^1 is hydrogen, alkyl, alkenyl, cyano, halogen, alkoxycarbonyl, $-CONR^9R^{10}$ can be prepared from the corresponding compounds of formula (I) where R^1 is hydroxy by following literature procedures described in Ortar. G., *Tett. Lett.*, **27**, 5541 (1986); Stille, J. K., *J. Org. Chem.*, **52**, 422, (1987); and Capri, W., *J. Org. Chem.*, **55**, 350, (1990).

Compounds of formula (I) where A is -CHOH-, $-CH_2-$, $-C=NOR^4-$ can be prepared from corresponding compounds of formula (I) where A is -C(O)-. These transformations can be carried out by reduction of the carbonyl group or by treatment with an appropriate hydroxy or alkoxyamine by methods well known in the field of organic chemistry.

The conversion of compounds of formula (I) where R^1 is methoxy and hydroxy to corresponding compounds of formula (I) where R^1 is hydroxy, cyano, and hydrogen respectively are described in Examples 4 and 5 respectively.

It will be recognized by one skilled in the art that these transformation are not limited to the R^1 position but may be carried out at other positions in the compound of formula (I).

The present invention also relates to pharmaceutical compositions comprising a pharmacologically effective amount of a compound of the present invention and a pharmaceutically acceptable excipient.

The compounds of the invention are useful as therapeutically active substances. They are inhibitors of prostaglandin G/H Synthase I and II (COX I and COX II), especially COX II, *in vitro*, and as such are expected to possess both anti-inflammatory and analgesic properties *in vivo*. See, for example, Goodman and Gilmans's „The Pharmacological Basis of Therapeutics", Ninth Edition, McGraw Hill, New York, 1996, Chapter 27. The compounds, and compositions containing them, are therefore useful as anti-inflammatory and

analgesic agents in mammals, especially humans. They find utility in the treatment of fever, inflammation and pain caused by conditions such as rheumatic fever, symptoms associated with influenza or other viral infections, low back and neck pain, dysmenorrhoea, headache, toothache, sprains, myositis, synovitis, arthritis (rheumatoid arthritis and osteoarthritis), gout, ankylosing spondylitis, bursitis, burns or injuries. They maybe used to inhibit prostanoid-induced smooth muscle contractions (e.g., in the treatment of dysmenorrhoea, premature labour and asthma) and to treat autoimmune disorders (such as systemic lupus erythematosus and type I diabetes).

Accordingly the present invention relates to compounds of formula I for use in the treatment of auto immune diseases, especially for systemic lupus erythematosus an type I diabetes or for use in the treatment of an inflammatory or auto immune disease.

As inhibitors of prostaglandin G/H Synthase, the compounds of this invention are also expected to be useful in the prevention and treatment of cancer, in particular colon cancer. It has been shown that COX-2 gene expression is upregulated in human colorectal cancers and that drugs that inhibit prostaglandin G/H Synthase are effective in animal models of cancer (Eberhart, C.E., *et. al.*, *Gastroenterology*, **107**, 1183-1188, (1994), and Ara, G. and Teicher, B.A., *Prostaglandins, Leukotrienes and Essential Fatty Acids*, **54**, 3-16, (1996)). In addition, there is epidemiological evidence that shows a correlation between use of drugs that inhibit prostaglandin G/H synthase and a reduced risk of developing colorectal cancer, (Heath, C.W. Jr., *et. al.*, *Cancer*, **74**, No. 10, 2885-8, (1994)).

The compounds of this invention are also expected to be useful in the prevention and treatment of Alzheimer's disease. Indomethacin, an inhibitor of prostaglandin G/H synthase, has been shown to inhibit the cognitive decline of Alzheimer's patients, (Rogers, J., *et. al.*, *Neurology*, **43**, 1609, (1993)). Also, the use of drugs which inhibit prostaglandin G/H synthase has been linked epidemiologically with a

delayed onset of Alzheimer's disease, (Breitner, J.C.S., *et. al.*, *Neurobiology of Aging*, **16**, No. 4, 523, (1995) and *Neurology*, **44**, 2073, (1994)).

The anti-inflammatory activity of the compounds of this invention may be assayed by measuring the ability of the compound to inhibit COX I and COX II, especially COX II, *in vitro*, using a radiometric assay, as described in more detail in Example 8. It may also be assayed by *in vivo* assays such as the Rat Carrageenan Paw and Rat Air-Pouch assays, as described in more detail in Examples 9 and 10. The analgesic activity of the compounds of this invention may be assayed by *in vivo* assays such as the Randall-Selitto assay and the rat arthritis pain model, as described in Example 11.

In general, the compounds of this invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of this invention, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

Therapeutically effective amounts of compounds of formula (I) may range from approximately 0.005-10 mg per kilogram body weight of the recipient per day; preferably about 0.05-1 mg/kg/day. Thus, for administration to a 70 kg person, the dosage range would preferably be about 3.5 mg to 70 mg per day.

In general, compounds of this invention will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen which can be adjusted according to

the degree of affliction. Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

The compositions are comprised of in general, a compound of formula (I) in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of formula (I). Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art .

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water,

ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

Other suitable pharmaceutical excipients and their formulations are described in *Remington's Pharmaceutical Sciences*, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

The level of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt%) basis, from about 0.01-99.99 wt% of a compound of formula (I) based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1-80 wt%. Representative pharmaceutical formulations containing a compound of formula (I) are described in Example 7.

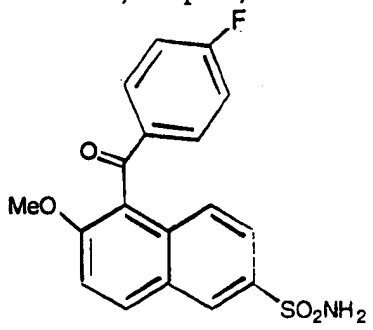
EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Abbreviations used in the examples are defined as follows: „HCl" for hydrochloric acid, „DMF" for dimethylformamide, „NaOH" for sodium hydroxide, and „DMSO" for dimethylsulfoxide.

Example 1

Synthesis of 5-(4-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide [following Scheme A, Steps 1, 2 and 3 (method B)]



Step 1

A solution of 2-methoxynaphthalene (20.0g, 120 mmol) and 4-fluorobenzoyl chloride (15 ml, 126 mmol) in methylene chloride (200 ml) was cooled in an ice bath under nitrogen and aluminum chloride (18.5 g, 129 mmol, 1.1 equiv.) was added portionwise over 10 minutes. The reaction mixture was stirred at room temperature for 3 h and then poured into 2N HCl (500 ml). The product was extracted into methylene chloride, and washed with brine, and dried over sodium sulfate. The organic layer was concentrated *in vacuo* to give 34.6g of 1-(4-fluorobenzoyl)-2-methoxynaphthalene as a solid (97% yield) which was used in the next step without further purification.

Step 2

1-(4-fluorobenzoyl)-2-methoxynaphhthalene (4.0 g, 14.2 mmol), [prepared as described in step 1], was dissolved in chlorosulfonic acid (10 ml). After stirring at room temperature for 15 minutes, the reaction mixture was carefully poured into ice and the product was extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give 5.39 g of 5-(4-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonyl chloride which was used in the next step without further purification.

Step 3

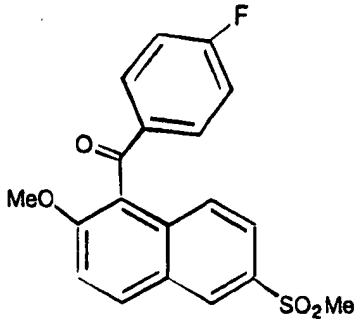
A solution of 5-(4-fluorobenzoyl)-6-methoxy-2-naphthalene-sulfonyl chloride (5.39g, 14.2 mmol), [prepared as described in step 2

above], in dioxane (100 ml), was cooled in an ice bath under nitrogen, and concentrated ammonium hydroxide (20 ml) was added dropwise. After 1h, the dioxane was removed under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic layer was separated and washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography (gradient elution, 20 - 60% ethyl acetate/hexane) and then recrystallized from ethyl acetate/hexane to afford 2.7 g of 5-(4-fluorobenzoyl)-6-methoxy-2-naphthalene-sulfonamide as white crystals.

Proceeding as described in Example 1 above, but substituting 4-fluorobenzoyl chloride in step 1, with:
benzoyl chloride;
4-chlorobenzoyl chloride;
4-methylbenzoyl chloride;
2-fluorobenzoyl chloride;
3-fluorobenzoyl chloride; and
4-acetoxybenzoyl chloride (prepared from 4-acetoxybenzoic acid); gave, respectively,
5-benzoyl-6-methoxy-2-naphthalenesulfonamide;
5-(4-chlorobenzoyl)-6-methoxy-2-naphthalenesulfonamide;
5-(4-methylbenzoyl)-6-methoxy-2-naphthalenesulfonamide;
5-(2-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide;
5-(3-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide; and
5-(4-hydroxybenzoyl)-6-methoxy-2-naphthalenesulfonamide.

Example 2

Synthesis of 5-(4-fluorobenzoyl)-6-methoxy-2-methylsulfonylnaphthalene (following Scheme D)



Step 1

A solution of 2-bromo-6-methoxynaphthalene (22.2 g, 93.6 mmol) in tetrahydrofuran (500 ml) was cooled to -78 °C and *n*-butyllithium (75 ml 1.6 M in THF, 121.7 mmol) was added dropwise over 15 minutes. After 0.5 h, dimethyl disulfide (13 ml, 140 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 16 h, 1N sodium hydroxide (100 ml) was added and the reaction mixture was stirred for 1 h. The organic layer was separated and washed with 1N sodium hydroxide, 5% aqueous sodium sulfite, and brine, and dried over sodium sulfate. The solvent was removed *in vacuo* and the crude product was recrystallized form ethyl acetate and hexane to give 11.1 g of 2-methoxy-6-methylthio-naphthalene as a solid (58 % yield).

Step 2

To a solution of 2-methoxy-6-methylthionaphthalene (1.0 g, 4.9 mmol), [prepared as described in Step 1], in methylene chloride (50 ml) was added 3-chloroperoxybenzoic acid (3.5 g, 10.3 mmol, 50-60%) portionwise. After 0.5 h, the reaction mixture was cooled in an ice bath, sodium sulfite (0.53 g, 4.2 mmol) was added and the stirring was continued for another 20 minutes. The reaction mixture was then poured in water and the organic layer was separated and dried over sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (gradient elution 30-

50% ethyl acetate/ hexanes) to give 930 mg of 2-methoxy-6-methylsulfonylnaphthalene (80% yield).

Step 3

To a solution of 2-methoxy-6-methylsulfonylnaphthalene (0.93 g, 3.93 mmol), [prepared as described in step 2 above], in 1,2-dichloroethane (40 ml) was added 4-fluorobenzoyl chloride (0.93 ml, 7.87 mmol) and aluminum chloride (1.05 g, 7.87 mmol) and the reaction mixture was heated at reflux. After 16 h, the reaction mixture was poured in 2N HCl and extracted into methylene chloride. The organic layer was separated and washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (gradient elution 10-60% ethyl acetate/ hexanes) to give 1.2 g of 5-(4-fluorobenzoyl)-6-hydroxy-2-methylsulfonyl-naphthalene as a tan solid (89% yield).

Step 4

A mixture of 5-(4-fluorobenzoyl)-6-hydroxy-2-methylsulfonyl-naphthalene (1.0 g, 2.9 mmol), [prepared as described in step 3 above], methyl iodide (0.65 ml, 10.45 mmol), and potassium carbonate (0.64 g, 4.65 mmol) in N,N-dimethylformamide (10 ml) was stirred at room temperature. After 16 h, the reaction mixture was diluted with water and extracted into ethyl acetate. The organic layer was separated, washed with brine, and dried over sodium sulfate. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (gradient elution 40-100% ethyl acetate/ hexanes) to give 1.0g of 5-(4-fluorobenzoyl)-6-methoxy-2-methylsulfonylnaphthalene as a solid (96% yield).

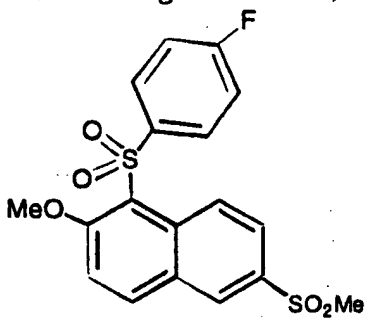
Substituting 4-fluorobenzoyl chloride with benzoyl chloride in step 3 of this example, gave a mixture of 5-benzoyl-6-methoxy-2-methylsulfonylnaphthalene and 5-benzoyl-6-hydroxy-2-methylsulfonylnaphthalene which were separated by flash chromatography (gradient elution 20-50% ethyl acetate /hexanes).

Proceeding as described in Example 2 above, but substituting 4-fluorobenzoyl chloride with 4-chlorobenzoyl chloride in step 3, gave a mixture of 5-(4-chlorobenzoyl)-6-methoxy-2-methylsulfonylnaphthalene and 5-(4-chlorobenzoyl)-6-hydroxy-2-methylsulfonylnaphthalene which were separated by flash chromatography.

Proceeding as described in Example 2 above, but substituting 4-fluorobenzoyl chloride with 2-fluorobenzoyl chloride in step 3, gave a mixture of 5-(2-fluorobenzoyl)-6-methoxy-2-methylsulfonylnaphthalene and 5-(2-fluorobenzoyl)-6-hydroxy-2-methyl-sulfonylnaphthalene which were separated by flash chromatography

Example 3

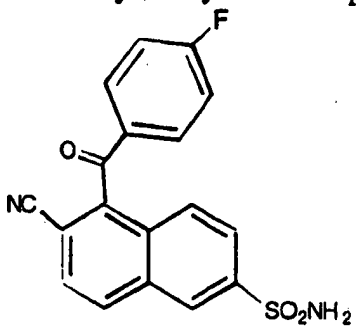
Synthesis of 5-(4-fluorophenylsulfonyl)-6-methoxy-2-methylsulfonylnaphthalene
(following Scheme D)



Aluminum chloride (1.13 g, 8.46 mmol) was added to a solution of 2-methoxy-6-methylsulfonylnaphthalene (1.0 g, 4.2 mmol) [prepared as described in example 2 above], and 4-fluorobenzenesulfonyl chloride (1.65 g, 8.46 mmol) in 1,2 dichloroethane (40 ml). The reaction mixture was heated at reflux for 16 h, and then poured into 2N HCl and extracted into methylene chloride. The organic layer was separated, washed with water and brine, and dried over sodium sulfate. Purification by flash chromatography gave 0.1g of 5-(4-fluoro-phenylsulfonyl)-6-methoxy-2-methylsulfonylnaphthalene as a solid (16% yield).

Example 4

Synthesis of 5-(4-fluorobenzoyl)-6-cyano-2-naphthalenesulfonamide



Step 1

Boron tribromide (55.7 ml, 1M solution in methylene chloride) was added to a suspension of 5-(4-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide (5 g, 14 mmol), [prepared as described in example 1], in methylene chloride (100 ml) at 0 °C. After 30 minutes, the reaction mixture was poured into brine and the product was extracted into methylene chloride. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to dryness *in vacuo*. The crude product was purified by chromatography (silica gel, gradient elution, 20-80% ethyl acetate /hexane) to afford 4.0 g of 5-(4-fluorobenzoyl)-6-hydroxy-2-naphthalenesulfonamide as a solid (83% yield).

Step 2

Pyridine (4.25 ml, 52.1 mmol) and trifluoromethanesulfonic anhydride (4.4 ml, 26.1 mmol) were added to a solution of 5-(4-fluorobenzoyl)-6-hydroxy-2-naphthalene-sulfonamide (3.0 g, 8.7 mmol), [prepared as described in step 1 above], in methylene chloride (50 ml) at 0 °C. After 0.5 h, 1N sodium bisulfate was added and the stirring was continued for an additional 30 minutes. The organic layer was separated, washed with brine, and dried over sodium sulfate. The solvent was removed *in vacuo* to give 3.1 g of 5-(4-fluorobenzoyl)-6-trifluoromethylsulfonyloxy-2-naphthalenesulfonamide as an oil (75% yield).

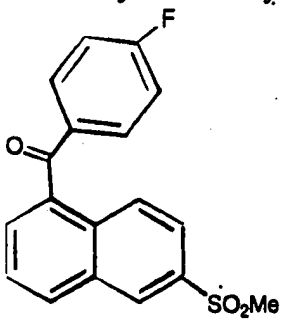
Step 3

A mixture of 5-(4-fluorobenzoyl)-6-trifluoromethyl-sulfonyloxy-2-naphthalene-sulfonamide (1.0 g, 2.1 mmol) [prepared as described in step 2 above,], potassium cyanide (0.15 mg, 2.3 mmol), and tetrakis(triphenylphosphine)palladium(0) in dioxane (15 ml) was heated at reflux under argon. After 2 h, the reaction mixture was cooled to RT, poured into brine, and the product was extracted into ethyl acetate. The organic layer was dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (gradient elution, 20-50% ethyl acetate /hexane) and then recrystallized from ethyl acetate-hexane to give 0.44 g of 5-(4-fluorobenzoyl)-6-cyano-2-naphthalene-sulfonamide as a white solid (54% yield).

Proceeding as described in Example 4 above, but substituting 5-(4-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide with 5-(2-fluorobenzoyl)-6-methoxy-2- naphthalene-sulfonamide gave 5-(2-fluorobenzoyl)-6-cyano-2-naphthalenesulfonamide.

Example 5

Synthesis of 5-(4-fluorobenzoyl)-2-methylsulfonylnaphthalene



Step 1

Pyridine (0.74 ml, 9.2 mmol) and trifluoromethanesulfonic anhydride (0.78 ml, 4.6 mmol) were added to a solution of 5-(4-fluorobenzoyl)-6-hydroxy-2-methylsulfonyl-naphthalene (0.4 g, 1.2 mmol), [prepared as described in example 2 above], in methylene chloride at 0 °C. After 0.5 h, 1N sodium bisulfate was added and the stirring was continued for an additional 30 minutes. The organic

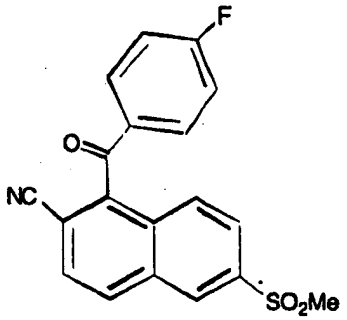
layer was separated, washed with brine, and dried over sodium sulfate. The solvent was removed *in vacuo* to give 0.62 g of 5-(4-fluorobenzoyl)-6-trifluoromethyl-sulfonyloxy-2-methylsulfonylnaphthalene as an oil.

Step 2

A mixture of 5-(4-fluorobenzoyl)-6-trifluoromethylsulfonyloxy-2-methylsulfonyl-naphthalene (0.3 g, 0.63 mmol), [prepared as described in step 1 above], formic acid (0.096 ml, 2.5 mmol), triethylamine(0.36 ml, 2.5 mmol), palladium acetate (14 mg, 0.06 mmol), and 1,3-bis (diphenylphosphino)propane (0.10 g, 0.03 mmol) in DMF (10 ml) was stirred at room temperature. After 16 h, the reaction mixture was poured into brine and extracted into ethyl acetate. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash chromatography (gradient elution 10-30% ethyl acetate / hexanes) and then recrystallized from ethyl acetate -hexanes to give 0.1 g of 5-(4-fluoro-benzoyl)-2-methylsulfonylnaphthalene as a solid (48% yield).

Example 6

Synthesis of 5-(4-fluorobenzoyl)-6-cyano-2-methylsulfonylnaphthalene



Step 1

Pyridine (0.38 ml, 4.65 mmol) and trifluoromethanesulfonic anhydride (0.39 ml, 2.32 mmol) were added to a solution of 5-(4-fluorobenzoyl)-6-hydroxy-2-methylsulfonyl-naphthalene (0.4 g, 1.16 mmol), [prepared as described in Example 2, step 3 above], in methylene chloride (10 ml) at 0 °C. After 0.5 h, additional amounts of

pyridine (0.38 ml, 4.65 mmol) and trifluoromethanesulfonic anhydride (0.39 ml, 2.32 mmol) were added and stirring was continued. After 0.5 h, 1N sodium bisulfate was added and the stirring was continued for an additional 30 minutes. The organic layer was separated, washed with brine, and dried over sodium sulfate. The solvent was removed *in vacuo* to give 0.6 g of 5-(4-fluorobenzoyl)-6-trifluoromethylsulfonyloxy-2-methylsulfonylnaphthalene as an oil (90 % yield).

Step 2

A mixture of 5-(4-fluorobenzoyl)-6-trifluoromethylsulfonyloxy-2-methylsulfonyl-naphthalene (2.5 g, 5.2 mmol) [prepared as described in step 1 above,], potassium cyanide (0.41 g, 6.3 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.30 g, 0.26 mmol) in dioxane (50 ml) was heated at reflux under argon. After 16 h, the reaction mixture was cooled to RT, poured into brine, and the product was extracted into ethyl acetate. The organic layer was dried with sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography (gradient elution, 10-60% ethyl acetate /hexane) and then recrystallized from ethyl acetate-hexane to give 1.16 g of 5-(4-fluorobenzoyl)-6-cyano-2-methylsulfonyl-naphthalene as a solid (63 % yield).

Proceeding as described in Example 6 above, but substituting 5-(4-fluorobenzoyl)-6-hydroxy-2-methylsulfonylnaphthalene with:

5-benzoyl-6-hydroxy-2-methylsulfonylnaphthalene;

5-(4-chlorobenzoyl)-6-hydroxy-2-methylsulfonylnaphthalene; and

5-(2-fluorobenzoyl)-6-hydroxy-2-methylsulfonylnaphthalene,

gave

5-benzoyl-6-cyano-2-methylsulfonylnaphthalene;

5-(4-chlorobenzoyl)-6-cyano-2-methylsulfonylnaphthalene; and

5-(2-fluorobenzoyl)-6-cyano-2-methylsulfonylnaphthalene,

respectively.

Proceeding as described in Example 6 above, but substituting potassium cyanide with trimethylaluminum in step 2, gave 5-(4-fluorobenzoyl)-6-methyl-2-methylsulfonyl-naphthalene.

Example 7

The following are representative pharmaceutical formulations containing a compound of formula (I).

Tablet formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this invention	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Capsule formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Suspension formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 ml
colorings	0.5 mg
distilled water	q.s. to 100 ml

Injectable formulation

The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	0.4 mg
sodium acetate buffer solution, 0.4 M	2.0 ml
HCl (1N) or NaOH (1N)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 ml

Example 8

Inhibition of COX I and COX II *in vitro*

The COX I and COX II inhibitory activity of compounds of this invention *in vitro* was determined using partially purified COX I and COX II enzymes, prepared as described in J. Barnett *et. al.*, *Biochim. Biophys. Acta*, **1209**, 130-139 (1994).

COX I and COX II samples were diluted with Tris-HCl buffer (50mM Tris-HCl, pH 7.9) containing 2 mM EDTA and 10% glycerol and reconstituted by incubating first with 2 mM phenol for 5 minutes and then with 1 micromolar hematin for an additional 5 minutes. 125 µl of the reconstituted COX I or COX II enzyme were preincubated for 10 minutes at room temperature in a shaking water bath with the compounds of the invention dissolved in 2-15 µl of DMSO or the carrier vehicles (control samples). The enzyme reaction was initiated by adding 25 µl of 1-[14 C]arachidonic acid (80,000-100,000 cpm/tube; 20 micromolar final concentration) and the reaction was allowed to continue for an additional 45 seconds. The reaction was terminated by adding 100 µl of 2N HCl and 750 µl water. An aliquot (950 µl) of the reaction mixture was loaded onto a 1 ml C_{18} Sep-Pak column (J.T. Baker, Phillipsburg, NJ) which had been previously washed with 2-3 ml methanol and equilibrated with 5-6 ml distilled water. Oxygenated products were quantitatively eluted with 3 ml of acetonitrile/water/ acetic acid (50:50:0.1, v/v) and the radioactivity in the eluate determined in a scintillation counter.

Compounds of this invention were active in this assay.

The COX inhibitory activities (expressed as IC_{50} , the concentration causing 50% inhibition of the COX enzyme being assayed) of some compounds of the invention and indomethacin as a comparator, were:

CPD #	COX I IC_{50}, μM	COX II IC_{50}, μM	CPD #	COX I IC_{50}, μM	COX II IC_{50}, μM
1	20	0.51	92	646	5.9
4	2.8	0.84	93	435.6	7.84
5	0.46	0.56	94	805	2.43
14	47.7	0.076	95	1000	2.73
15	62.5	0.68	96	>100	0.80
20	6.0	0.45	97	>100	0.80
42	40.9	2.0	99	>100	0.5
64	0.9	0.7	100	>100	0.25
65	300	0.7	103	97	1.5
66	100	0.3	104	93	0.57
91	90.8	0.92	Indo-methacin	0.4	14

Example 9

Anti-inflammatory activity

The anti-inflammatory activity of compounds of this invention was determined by measuring the inhibition of carrageenan-induced paw edema in the rat, using a modification of the method described in Winter C. A. *et al.*, „Carrageenan-Induced Edema in Hind Paw of the Rat as an Assay for Anti-inflammatory Drugs" *Proc. Soc. Exp. Biol. Med.* 111, 544-547, (1962). This assay has been used as a primary *in vivo* screen for anti-inflammatory activity of most NSAIDs, and is considered predictive of human efficacy. Briefly, test materials were administered orally to female rats in a volume of 1 ml prepared as solutions or suspensions in an aqueous vehicle containing 0.9% sodium chloride, 0.5% sodium carboxymethyl-cellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol and 97.3% distilled water. Control rats received vehicle alone. After 1 h 0.05 ml of a 0.5% solution of Carrageenan (Type IV Lambda, Sigma Chemical Co.) in 0.9% saline was injected into the subplantar region of the right hind paw. Three

hours later the rats were euthanized in a carbon dioxide atmosphere; hind paws were removed by severing at the tatso-crural joint; and the left and right paws were weighed. The increase in weight of the right paw over the left paw was obtained for each animal and the mean increases were calculated for each group. The anti-inflammatory activity of the test materials is expressed as the percent inhibition of the increase in hind paw weight of the test group relative to the vehicle dosed control group.

Compounds of this invention were active in this assay.

The anti-inflammatory activities (expressed as % inhibition) of some of the compounds of the invention were:

CPD #	Dose mg/Kg	% Inhibition	CPD #	Dose mg/Kg	% Inhibition
1	10	29.94	91	10	29.48
4	10	26.41	92	30	19.88
5	30	27.49	93	30	6.25
17	30	19.56	95	30	15.5
20	30	33.85	96	30	38
64	6	30	97	30	40
65	12	30	99	10	38
66	12	30	104	30	33

Example 10

Inhibition of eicosanoid synthesis *in vivo*

The activity of compounds of this invention in inhibiting *in vivo* eicosanoid (prostaglandin E_2) synthesis in inflamed tissues was determined by the carrageenan-induced inflammation (air-pouch model) in rats, using a modification of the method described in Futaki, M., *et al.*, „Selective Inhibition of NS-398 on prostanoid production in

inflamed tissue in rat Carrageenan Air-pouch Inflammation" *J. Pharm. Pharmacol.* **45**, 753-755, (1993) and Masferrer, J. L., *et al.*; „Selective Inhibition of inducible cyclooxygenase 2 *in vivo* is Antiflammatory and Nonulcerogenic" *Proc. Natl. Acad. Sci. USA.* **91**, 3228-3232, (1994). In this assay, an air-pouch is created in the rat and the PGE_2 levels in the air-pouch exudate are measured by enzyme immunoassay. Briefly, male rats were anesthetized using a 60:40 CO_2:O_2 mixture and subsequently injected subcutaneously with 20 ml of sterilized air, under aseptic conditions, in the proximal area of the dorsum. This injection of sterile air causes the creation of a subcutaneous "air pouch". The next day, a further 10 ml of sterile air was injected into the previously formed pouch using the same technique. The test materials were administered orally in a volume of 1ml/100g body weight as solutions or suspensions in an aqueous vehicle containing 0.9% sodium chloride, 0.5% sodium carboxymethyl-cellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol and 97.3% water. Control rats received vehicle alone. After 30 minutes, 5 ml of a 0.5% solution of carrageenan (Sigma, Lambda Type IV) was injected into the air pouch. The rats were euthanized 3 or 6 h after the compound administration. 10 ml of a solution containing 10 mg/l of indomethacin and 5.4 mM EDTA in 0.9% sterile saline was injected into the air pouch; the air pouch was cut open; and the exudate was harvested. The total exudate volume was recorded, and the samples were analyzed for PGE_2 and 6-keto PGF_1 by ELISA (Titerzyme ', PerSeptive Diagnostics, Boston, MA) and TxB_2 by radioimmuno assay (New England Nuclear Research, Boston MA, Catalog No. NEK-037), according to the manufacturer's directions.

The mean concentrations of PGE_2 were calculated for each group. The anti-inflammatory activity of test materials is expressed as the percent inhibition of PGE_2 formation in the test group relative to the control group.

Compounds of this invention were active in this assay.

The anti-inflammatory activities (expressed as % inhibition of air pouch PGE_2 formation) of some of the compounds of this invention and indomethacin as a comparator were:

CPD #	Dose mg/Kg	% Inhibition	CPD #	Dose mg/Kg	% Inhibition
1	10	92	91	30	58.1
4	10	74.6	94	10	17.6
14	10	58.8	96	1	90
20	10	100	97	3	90
23	10	70.7	99	3	86
64	0.5	50	100	3	63
65	2	50	104	1	76.5
66	1	50	Indo-methacin	2-5	>70%

Example 11

Analgesic Activity

The analgesic activity of the compounds of this invention may be determined by using a modification of the method described in Randall, L. O., and Selitto, J. J., „ A Method for Measurement of Analgesic Activity on Inflamed Tissue", *Arch. Int. Pharmacodyn.*, CXI, 4, 409, (1957) and Gans, *et. al.*, „ Anti-Inflammatory and Safety Profile of DuP 697, a Novel Orally Effective Prostaglandin Synthesis Inhibitor", *J. Pharmcol. Exp. Ther.*, **254**, No. 1, 180, (1990). In this assay, the male Sprague Dawley rats were injected with 0.1 ml of 20% brewer's yeast in deionized water (Sigma, St. Louis) in the subplantar region of the left hind foot. After 2 h, the test materials were administered orally in a volume of 1 ml/100g body weight as solutions or suspensions in an aqueous vehicle containing 0.9% sodium chloride, 0.5% sodium carboxymethyl-cellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol and 97.3% water. Control rats received vehicle alone. After 1 h, the hindpaw was placed on the platform of a Basile Analgesy-Meter (Ugo Biological Research Apparatus, Italy, Model #

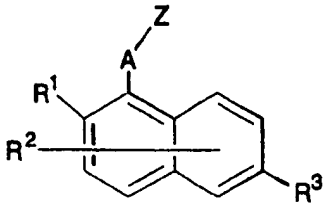
7200) and mechanical force was applied to the dorsum of the rat's hindpaw. Compounds of the invention were active in this assay.

The analgesic activity of compounds of this invention may also be determined by using an adjuvant-induced arthritis pain model in the rat, where pain is assessed by the animal's vocal response to the squeezing or flexing of an inflamed ankle joint, as described in Winter C.A. and Nuss, G.W., „Treatment of Adjuvant Arthritis in rats with Antiinflammatory Drugs", *Arthritis Rheum.*, **9**, 394-403, (1966) and Winter, C.A., Kling P.J., Tocco, D.J., and Tanabe, K., „Analgesic activity of Diflunisal [MK-647; 5-(2,4-Difluorophenyl)salicylic acid] in Rats with Hyperalgesia Induced by Freund's Adjuvant", *J. Pharmacol. Exp. Ther.*, **211**, 678-685, (1979).

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

Claims

1. A compound of the formula (I):

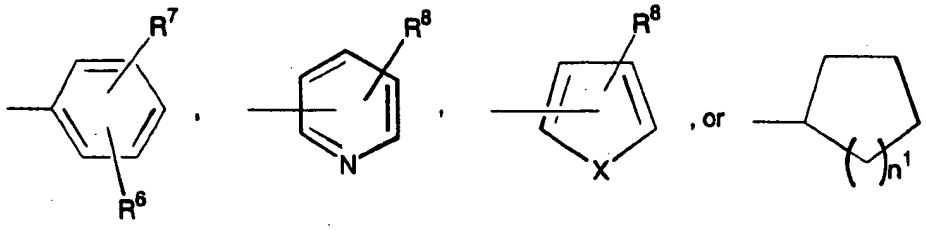


(I)

wherein:

A is a bond, $-CH_2-$, $-CH(OH)-$, $-C=NOR^4-$, $-C(O)-$, $-NR^5-$, $-O-$, or $-S(O)_n-$ where n is an integer from 0 to 2, R^4 is hydrogen or alkyl, and R^5 is hydrogen, alkyl, or acyl;

Z is a group represented by formula (B), (C), (D), or (E):



(B) (C) (D) (E)

where:

n^1 is 0 to 3;

X is O or S;

R^6 and R^7 are independently selected from hydrogen, alkyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, acyl, alkylthio, cycloalkylthio, cycloalkylalkylthio, alkoxy, cycloalkyloxy, cycloalkylalkyloxy, halogenalkyloxy, alkenyl, halogen, cyano, nitro, hydroxy, or $-NR^9R^{10}$ where R^9 and R^{10} are independently hydrogen, alkyl, or acyl; or R^6 and R^7 when they are adjacent to each other form methylenedioxy or ethylenedioxy;

R^8 is hydrogen, alkyl, halogenalkyl, alkoxy, cycloalkyloxy, halogenalkyloxy, alkylthio, cycloalkylthio, nitro, cyano, hydroxy, or halogen;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, halogenalkyloxy, hydroxyalkyloxy, alkoxyalkyloxy, alkylthio, cycloalkylthio, cycloalkylalkylthio, hydroxy, halogen, cyano, carboxy, alkoxycarbonyl, acyl, $-C=NOR^4$, $-NR^9R^{10}$, $-CONR^9R^{10}$, $-OCONR^9R^{10}$, or $-OSO_2R^{11}$ where R^4, R^9, and R^{10} are as previously defined and R^{11} is alkyl, cycloalkyl, or halogenalkyl;

R^2 is hydrogen, alkyl, alkoxy, halogen, nitro, or $-NR^9R^{10}$; and

R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ where:

R^{12} is alkyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, or alkoxycarbonylalkyl;

R^{13} is hydrogen, alkyl, or acyl; and

R^{14} is hydrogen, alkyl, halogenalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, amino, aminoalkyl, aryl, aralkyl, heteroaralkyl, heterocyclo, heterocycloalkyl, acyl, hydroxy, or alkoxy; or R^{13} and R^{14} together with the nitrogen atom to which they are attached optionally form a heterocycloamino group; and

their pharmaceutically acceptable salts, prodrugs, individual isomers, and mixtures of isomers.

2. A compound according to claim 1, wherein A is $-C=NOR^4-$, -O-, -S-, $-NR^5-$ or C(O)-.

3. A compound according to claim 1 or claim 2, wherein Z is a group represented by formula (B) or (D).

4. A compound according to any one of claims 1-3, wherein A is -C(O)-.

5. A compound according to any one of claims 1-4, wherein R^3 is $-SO_2R^{12}$ or R^3 is $-SO_2NR^{13}R^{14}$.

6. A compound according to claim 5, wherein:

Z is a group represented by formula (B) where R^6 and R^7 are independently selected from hydrogen, alkyl, cycloalkyl, alkoxy, ethenyl, halogen, or $-NR^9R^{10}$ where R^9 and R^{10} are alkyl, and R^2 is hydrogen.

7. A compound according to claim 5 or claim 6, wherein R^3 is $-SO_2$-(alkyl) or when R^3 is $-SO_2NR^{13}R^{14}$, R^{13} is $-SO_2NHR^{14}$ where R^{14} is hydrogen, alkyl, hydroxy, or 2-hydroxyethyl.

8. A compound according to any one of claims 5-7, wherein:

R^1 is hydrogen, alkyl, alkoxy, cycloalkoxy, 2-hydroxyethyloxy, hydroxy, halogen, or cyano; and R^6 and R^7 are independently hydrogen, alkyl, alkoxy, or halogen.

9. A compound according to claim 8, wherein:

R^1 is hydrogen, methyl, hydroxy, methoxy, chloro, or cyano; and R^3 is $-SO_2Me$ or SO_2NH_2.

10. A compound according to any one of claims 5-9, wherein R^6 and R^7 are independently selected from hydrogen, methyl, methoxy, fluoro, or chloro.

11. A compound according to any one of claims 6-10, wherein R^6 is at the 2-position and R^7 is at the 4-position or wherein R^6 is at the 3-position and R^7 is at the 4-position.

12. A compound according to claim 1, wherein R^1 is cyano, and R^6 and R^7 are hydrogen namely, 5-benzoyl-6-cyano-2-methylsulfonylnaphthalene.

13. The compound according to claim 1, wherein R^1 is cyano, R^6 is hydrogen, and R^7 is fluoro namely, 5-(4-fluorobenzoyl)-6-cyano-2-methylsulfonylnaphthalene.

14. The compound according to claim 1, wherein R^1 is methoxy, R^6 is hydrogen, and R^7 is fluoro namely, 5-(4-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide.

15. The compound according to claim 1, wherein R^1 is cyano, R^6 is hydrogen, and R^7 is fluoro namely, 5-(4-fluorobenzoyl)-6-cyano-2-naphthalenesulfonamide.

16. The compound according to claim 1, wherein R^1 is methoxy, R^6 is fluoro, and R^7 is hydrogen namely, 5-(3-fluorobenzoyl)-6-methoxy-2-naphthalenesulfonamide.

17. A compound according to any one of claims 1-4, wherein:

Z is a group represented by formula (D) where X is S and is linked to A at the 2-position of (D); and R^2 and R^8 are hydrogen.

18. A compound according to claim 17, wherein R^3 is $-SO_2R^{12}$ or $-SO_2NR^{13}R^{14}$ where:

R^{12} is alkyl; R^{13} is hydrogen; and R^{14} is hydrogen, alkyl, hydroxy, or 2-hydroxyethyl.

19. A compound according to claim 17 or claim 18, wherein R^1 is hydrogen, alkyl, alkoxy, cycloalkoxy, 2-hydroxyethyloxy, hydroxy, chloro, or cyano.

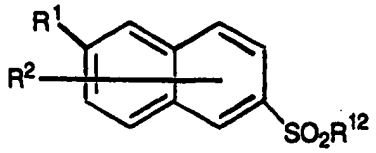
20. A compound according to claim 19, wherein:

R^3 is $-SO_2Me$ or $-SO_2NH_2$; and R^1 is hydrogen, methyl, hydroxy, methoxy, chloro, or cyano.

21. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according in any one of claim 1-20 and a pharmaceutically acceptable non-toxic excipient.

22. A process for preparing a compound of claim 1 wherein A is -C(O)-, which comprises:

(1) reacting a compound of the formula



where R^1, R^2 and R^{12} are as defined in claim 1, with an acylating agent of formula ZC(O)L where L is a leaving group under acylating conditions and Z is as defined in claim 1; and

(2) optionally modifying any of the R^1, R^2, R^6, R^7, R^8 and R^{12} groups.

23. Compounds according to any one of claims 1-20 for use as a therapeutically active substance.

24. Compounds according to any one of claims 1-20 for use in the treatment of an inflammatory disease, especially for myositis, synovitis, gout, ankylosing spondylitis, bursitis and arthritis preferably rheumatoid arthritis and osteoarthritis.

25. Compounds according to any one of claims 1-20 for use in the treatment of an autoimmune disease, especially for systemic lupus erythematosus and type I diabetes.

26. The use of a compound according to any one of claims 1-20 in the treatment of an inflammatory or autoimmune disease.

27. The use of a compound according to any one of claims 1-20 in the preparation of a medicament for the treatment of an inflammatory or autoimmune disease.

28. The novel compounds, intermediates, compositions processes and uses substantially as herein before described.

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INTERNATIONAL SEARCH REPORT

	ational Application No
	PCT/EP 98/00306

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C311/29 C07C317/24 C07C317/22 C07C311/51 C07D295/12
C07D213/42 A61K31/18 A61K31/10 A61K31/275 A61K31/235
A61K31/435 //C07D307/52,C07C311/53,C07D211/58,C07D405/04,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 899 529 A (B.E. WITZEL) 12 August 1975 cited in the application see column 1, line 1 - column 4, line 27; column 11, lines 48-53 *	1,21,23, 24,26,27
A	CH 384 567 A (J.R. GEIGY AG) 15 February 1965 see page 1, line 1 - line 37	1,21,23
A	EP 0 354 329 A (BAYER AG) 14 February 1990 see claims 1-3	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 1998	09.06.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

arnational Application No
PCT/EP 98/00306

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/26,C07D295/22,C07D211/96,C07D317/44,C07D333/22,C07D307/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 1998	09.06.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

.ternational application No.
PCT/EP 98/00306

Box I Obs rvation where certain claims were found un ear hable (Continuati n f Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 26 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 28
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

The compounds, intermediates, compositions, processes and uses claimed in claim 28 are not defined and hence could not be searched.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ırnational Application No
PCT/EP 98/00306

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EP 354329 A	14-02-1990	DE 3823318 A	22-02-1990
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